MICROMACHINED STIMULATING MICROELECTRODE ARRAYS

Quarterly Report #3

(Contract NIH-NINDS-NO1-NS-9-2304)

October - December 1999

Submitted to the

Neural Prosthesis Program

National Institute of Neurological Disorders and Stroke
National Institutes of Health

by the

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January 2000

MICROMACHINED STIMULATING MICROELECTRODE ARRAYS

Summary

This contract seeks to develop a family of thin-film stimulating arrays for use in neural prostheses. STIM-2B/-3B are two- and three-dimensional arrays of stimulating sites on 400µm centers. The probes have four channels and 64-sites. Any selected site can be used for either recording or stimulation. Current generation is off-chip. The high-end probes STIM-2/-3 are similar except they use on-chip current generation via 8-bit digital to analog converters.

During the past term, we have continued to fabricate passive probes for a variety of users and have begun to tackle the detailed problems associated with testing the active probes prior to use. Using the external user interface system, a test probe was tested with over 60 million pulses without failure, addressing the probe at the maximum rate achievable by the external board (9.5MHz). Additional long-term tests of these probes, running over one billion 100µA current pulses, will be performed during the coming term. Work on appropriate testing jigs and testing software protocols has reduced the testing time for the STIM-2B active probe from typically 5 hours to less than 1 hour per probe, and additional work in these areas is expected to reduce the testing time per probe to less than 10 minutes.

Work to determine efficient methods for activating the sites on active probes has explored parallel activation, serial activation, and a combination of the two in which the sites are activated in parallel nearly all the way to the desired level and then are finished serially. The greatest variation (site-to-site) when activating in parallel was 3.95%, whereas it was less than 0.5% with careful serial activation.

We are now beginning a design iteration on the high-end 64-site 8-channel STIM-2 probe, redesigning the DAC, adding multi-level interpulse voltage biasing, and adding separate dedicated output lines for recording mode. During the past term the DAC has

been redesigned to increase the bias current and ensure fast response. Additional design modifications are expected to be completed during the coming term.

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1. Introduction

The goal of this contract is the development of active multi-channel arrays of stimulating electrodes suitable for studies of neural information processing at the cellular level and for a variety of closed-loop neural prostheses. The probes should be able to enter neural tissue with minimal disturbance to the neural networks there and deliver highly-controlled (spatially and temporally) charge waveforms to the tissue on a chronic basis. The probes consist of several thin-film conductors supported on a micromachined silicon substrate and insulated from it and from the surrounding electrolyte by silicon dioxide and silicon nitride dielectric films. The stimulating sites are activated iridium, defined photolithographically using a lift-off process. Passive probes having a variety of site sizes and shank configurations have been fabricated successfully in past contracts and have been distributed to a number of research organizations nationally for evaluation in many different research preparations. For chronic use, the biggest problem associated with these passive stimulating probes concerns their leads, which must interface the probe to the outside world. Even using silicon-substrate ribbon cables, the number of allowable interconnects is necessarily limited, and yet a great many stimulating sites are ultimately desirable in order to achieve high spatial localization of the stimulus currents.

The integration of signal processing electronics on the rear of the probe substrate (creating an "active" probe) allows the use of serial digital input data which can be de-multiplexed on the probe to provide access to a large number of stimulating sites from a very few leads. Our goal in this area is to develop a family of active probes capable of chronic implantation in tissue. For such probes, the digital input data must be translated on the probe into per-channel current amplitudes that are then applied to the tissue through the sites. Such probes generally require five external leads, virtually independent of the number of sites used. As discussed in previous reports, we have designed a series of active probes containing CMOS signal processing electronics. Two of these probes have been completed and are designated as STIM-1A and STIM-1B. A third probe, STIM-2, is now beginning a final iteration and is a second-generation version of our original high-end first-generation design, STIM-1. All three probes provide 8-bit resolution in digitally setting the per- channel current amplitudes. STIM-1A and -1B offer a biphasic range using ±5V supplies from 0µA to ±254µA with a resolution of 2µA, while STIM-2 has a range from 0 to ±127µA with a resolution of 1µA. STIM-2 offers the ability to select 8 of 64 electrode sites and to drive these sites independently and in parallel, while STIM-1A allows only 2 of 16 sites to be active at a time (bipolar operation). STIM-IB is a monopolar probe, which allows the user to guide an externally-provided current to any one of 16 sites as selected by the digital input address. The high-end STIM-2 contains provisions for numerous safety checks and for features such as remote impedance testing in addition to its normal operating modes. It also offers the option of being able to record from any one

of the selected sites in addition to stimulation. It will be the backbone of a multi-probe three-dimensional (3D) 1024-site array (STIM-3) now in development. A new probe, STIM-2B, has recently been added to this set. It offers 64-site capability with off-chip generation of the stimulus currents for four separate channels. These channels are organized in four groups so that each current can be directed to any of the 16 sites in its group. Each selected channel can be programmed for either stimulation or recording. On-chip recording amplifiers offer a gain of 50; alternatively, the neural activity can be recorded using off-chip amplifiers interfaced through the normal stimulating channels. This probe is available in both 2D and 3D versions (as STIM-2B/3B) and is now being used in-vivo.

During the past quarter, we have continued to fabricate passive probe structures for a variety of users. We have also begun to tackle the testing challenges on the active probes and have evaluated various activation approaches possible for the sites. Long-term in-vitro testing of the active probes together with the external user interface has been pursued, and we have evaluated batch activation techniques for the probes in some detail. has also begun. Finally, we have started a final pass at the probes STIM-2 and STIM-3 (the 3D counterpart of STIM-2), seeking to add additional features and to correct shortcomings of the previous design. The results in each of these areas are described more fully in the sections below.

2. Passive Probe Developments

During the past quarter, three additional wafers from the STANDARDS mask set were completed with iridium sites. While probes from this mask set continue to satisfy the needs of most Center for Neural Communication Technology (CNCT) and NPP users, the resource Center continues to get requests from users with special preparations that require custom designs. Design and layout for two new passive probe mask sets is currently underway and fabrication should commence in the coming quarter.

As indicated in the companion report on Thin-Film Recording Microelectrodes, the first mask uses standard design rules and includes designs for Charles Miller and Paul Abbas of the University of Iowa for recording from the VIII nerve of the cat; Sandy Bledsoe of the University of Michigan for recording and stimulation in the guinea pig IC, David Edell of InnerSea Technology for interfacing between various devices and for testing encapsulation; Christophe Pouzat and Leslie Kay of Caltech for recording from olfactory bulb in the rat; Mark Knuepfer for recording from regenerated sympathetic nerve in rat; and Wayne Aldridge of the University of Michigan for recording from output structures of the rat basal ganglia.

The second mask set will incorporate smaller minimum features (1.5µm as opposed to the standard 3µm) to realize higher density, single-shank probes. The designs were submitted by CNCT collaborators Phil Hetherington, Tim Blanche and Nicholas Swindale of the University of British Columbia for 3-D cell localization and 2-D current

source density analysis in cortex. These probes will have up to 64 sites on a single shank arranged in two or three staggered rows on a substrate that is less than 250µm wide.

3. Active Stimulating Probe Development

The active stimulating probe development has seen some results of chronic pulse testing of the STIM-2B probe design. More probes have been etched out allowing the continued investigation of the best activation method for active stimulating probes by comparing CV curves. The etched out probes have been comprehensively tested and we are looking into the best method of improving the speed of testing. Clearly this will be an issue as we move to supply such probes to others, and several approaches are being explored, including building in additional circuitry to assist with the testing function on the probe itself.

STIM-2B

STIM-2B is a second-generation probe, a version of our simplest active stimulating probe, STIM-1B. STIM-2B is a four-channel, 16-shank, 64-site probe which routes four externally generated stimulus signals to 1-of-16 sites per channel. The fabrication of the CMOS circuitry has been completed and the digital functionality of the circuitry has been verified through testing of the different modes of the probe: POR, site selection, amplifier selection, and so forth. Testing of the analog amplifier has demonstrated that it too works quite well *in-vitro*, though *in-vivo* operation has been problematic due to the large DC drifts at the iridium sites.

The functionality of the STIM-2B probe is expected to provide an important tool for performing some very important and interesting experiments by allowing acute and chronic stimulation access to a relatively large volume of neural tissue without mechanically repositioning the probe. This capability is realized by utilizing a 20b shift register to load four 4b site addresses which are decoded by a 1-of-16 nand-type decoder to connect the desired site to an analog input/output pad through a large CMOS passgate transistor, thereby allowing the 'steering' of externally generated currents to the addressed site. A recording function is included and is addressed by a fifth bit included with the 4b site address. This fifth bit selects between stimulation mode and recording mode by selecting either a direct path to the I/O pad from the site or a path through an amplifier for recording from the same site. Each I/O channel has its own dedicated amplifier so that the functionality of all of the channels is fairly independent of each other except for the up-front data input circuitry.

Chronic In-Vitro Testing

Long-term pulse testing of the STIM-2B probes has been performed using the external interface system. Through a simple alteration of the software, the number of pulses is counted while the system continuously sends pulses through the probe under test. In order to verify that everything was working properly, an HP 53132A universal counter was connected to the output of the system as well. Initially, it was found that the count on the external counter did not exactly match the count on the system. This mismatch was traced to a faulty oscilloscope used to monitor the waveforms visually. The power on the oscilloscope would flicker occasionally due to a faulty power switch causing enough noise to be coupled back into the lead such that the counter triggered additional pulse counts.

With that problem removed from the circuit, a test-probe was pulsed with over 60 million voltage pulses without failure of the external system or the probe. The protocol is such that the probe is sent the site addresses and then the sites are pulsed 32,767 times. This is repeated continuously until interrupted by the operator. This method of re-addressing the probe, even though it is the same address, was used in order to also test the PC to external interface board serial communication link and the on-chip electronics. In future tests, we will likely increase the frequency of re-addressing the electronics in order to test the longevity of the digital portion of the circuitry as well. This does decrease the speed of the pulse testing because of the communication time required between pulses, which must occur both over the serial link and then to the probe. Since the probe is being addressed at the maximum rate (9.5MHz) achievable by the interface board, the serial link is by far the slowest step because of the amount of data to be transferred and the relatively low bit rate of 38,400 baud. This is the maximum rate that the software will currently support, but some rewriting may be able to increase this rate significantly. It is not yet known if the hardware will be able to reliably support serial data rates of 56k or even 115k but we expect that it could.

Long-term pulse testing will continue by utilizing a fully functional probe to deliver current pulses at the maximum rated amplitude of 100μA. Only 4 sites will actually be used to deliver current, one per channel. CV measurements of the characteristics of the sites will be made prior to starting and periodically thereafter. The amount of leakage current will be observed by monitoring the supply current periodically. A PCB interconnect with circuitry for both current delivery and for supply current monitoring is being built specifically for this purpose. Each probe tested should provide a significant amount of data since there are up to sixteen sets of four sites each which can be tested.

Functionality Testing

During the past quarter, additional STIM-2B probes have been released from a quarter of one wafer, carrying out final wafer thinning and release in the EDP etchant. The results of these final process steps are becoming more successful with each repetition. Probes from this batch have been visually inspected and sorted, mounted and wire bonded

onto PCB stalks. The new probes have also been comprehensively tested. Some of the testing was delayed due to a previously unnoticed problem with one of the external interface boards. A consistent problem with every probe tested eventually led to the discovery of the problem seen in Fig. 1. The normally 0-5V data signal, as seen in the bottom trace, was actually ~0-7.5V with a short deviation to about –2-(-2.5)V rather than just returning to ground. The ringing that can be seen in both the clock signal (upper trace) and the data signal are an artifact of the mismatched load impedance of the input of the oscilloscope to the connecting cable.

Using a different external interface board solved the data signal problem and the previously 'faulty' probes functioned correctly as expected. The faulty board may have contributed to the failure of several experiments since it may not have been properly scanning through or addressing the probe sites as it should have been. In the future, proper functionality of the external interface boards will be verified before each experiment. The actual source of the problem with the faulty board is not known at this point, but will be investigated further in the future. While testing with a properly functioning board, the probes were found to be capable of normal operation at data entry rates of up to 9.5MHz which is the maximum speed of the external interface system. All testing was subsequently performed at 9.5MHz. It should be noted that no apparent permanent damage to the probes was observed as a result of the excessively high (and low) data signal.

Previously, each of the STIM-2B probes was not necessarily tested comprehensively; that is, each site was not tested while stepping through all of the site addresses for that particular channel. Instead, several representative sites were tested and it was assumed that the remainder worked properly. Because it has been deemed necessary to know without any uncertainty which sites are being accessed and which sites are working properly during any experiments, the testing is now being done comprehensively. A possible problem, which may have gone otherwise undetected, can be seen in the test matrix of Fig. 2. The X's indicate that a signal (pulse) is observed at the physical site (horizontal) when the indicated address (vertical) is loaded. The 0's indicate that no signal was observed at the physical when the proper address was loaded. Sites with more than one X in the column are activated by more than one address. The pattern observed indicates that the problem is a *stuck* complement of the second bit. This type of functionality is obviously not desirable because of more than one site being selected for a given address. For example, if the address for site four is loaded, not only will site four be accessed; site six will also be accessed. This would lead to a dividing of the stimulus current between those two sites in the stimulation mode, or a mixing of the signal from both sites in the case of recording. Ideally, all channels of a probe will have the test matrix of Fig. 3, where each site is accessed only by its own address.

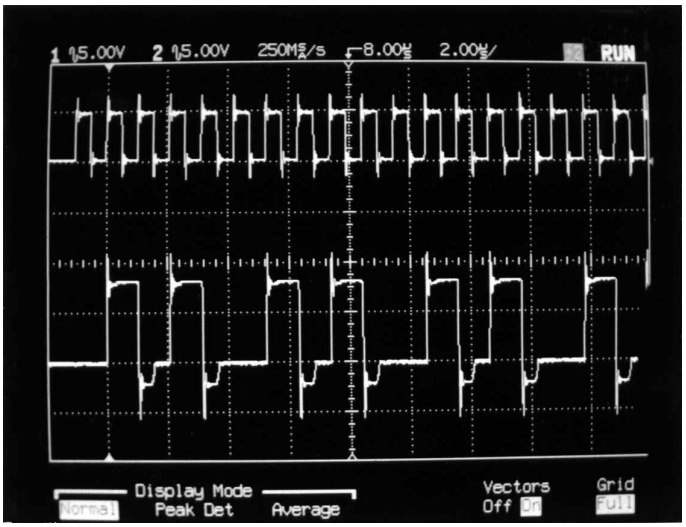

Fig. 1: An oscilloscope trace which shows the clock (upper trace) and the faulty data signal (lower trace) deviating from the normal 0-5V logic levels.

				Channel D												
Address\Site	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0	X		X													
1		X		X												
2			X													
3				X												
4					X		X									
5						X		X								
6							X									
7								X								
8									0							
9										X		X				
10											0					
11												X				
12													X		X	
13														X		X
14															X	
15																X

Fig. 2: The test matrix for Channel D of probe #2004 shows the type of functional problem that may go unnoticed without comprehensive testing. A *stuck* complement of the second bit results in sites that are accessed by two addresses. The 0's indicate a site that did not work for any address.

Functionality	Max Freq.						Test Freq.									
	9.5MHz						9.5MHz									
				Channel A												
Address\Site	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0	X															
1		X														
2			X													
3				X												
4					X											
5						X										
6							X									
7								X								
8									X							
9										X						
10											X					
11												X				
12													X			
13														X		
14															X	
15																X

Fig. 3: The test matrix for Channel A of probe #2000 demonstrates a properly functioning probe channel. All of the channels of probe #2000 function in this manner.

Initially, the comprehensive testing was a very time consuming process (4-6 hours per probe) because it was necessary to make contact to each site with a metal circuit probe and then manually pulse the appropriate channel while selecting through the site addresses. Some alteration of the external interface software, which now automatically cycles through the site addresses, has cut the testing time per probe to ~1-1.5 hours, depending on how well the probe functions. The limiting factor is now the process of manually contacting each site with a metal circuit probe. Eventually, if these probes are to be produced in any appreciable quantity, the amount of time required to test each probe will have to be reduced considerably and this can only be done through automation. In order to automate the testing, a method of either simultaneously contacting all of the sites or automatically, serially contacting and testing one or more of the sites will have to be developed. The later option, automatic site probing, would be very difficult and expensive; therefore, is not considered realistic.

It may be possible to test the probes on the wafer prior to being released in the final EDP etch by utilizing a probe-card which has an array of metal circuit probes for simultaneously contacting all of the sites. The STIM-2B probes that do not pass the wafer-level functionality test could be marked appropriately, but there is still the possibility that a functional probe would no longer be fully functional after the etch-out process. Therefore, the probes would have to be tested again after etch-out. Because of the flexibility of the probe shanks, a probe-card could not easily used on released probes unless the shanks are backed by or held against something solid. This type of arrangement

has the potential to result in more breakage of the shanks unless the shank support were made of a material soft enough to 'give' slightly.

We are looking into this problem of comprehensively and quickly testing the complete functionality of active probes with large arrays of sites. This problem is not peculiar to active stimulation probes; it is also a problem that needs to be solved in order to rapidly test active recording probes as well. There are a number of methods of testing being considered. As previously mentioned, there is the possibility of probe-card contact to all of the sites simultaneously. Another possible method would be to place another silicon probe near the sites in saline or a similar conductive environment thereby allowing the signal to be monitored in the proximity of a site. There are also several methods being considered that would involve micromachining jigs with integrated contact points for contacting all of the sites simultaneously. This may be a very interesting and technical method of solving the problem, but it may not be the simplest or the most practical.

Whatever the final solution is, it will require a good connection between the probe sites and the testing leads, whether it be made by physical contact or by fluid/ionic connection. The use of a fluidic/ionic contacts would be beneficial especially if it ever became necessary to retest a probe whose iridium sites had already been activated. Activating the iridium of the probe sites makes it very difficult to make an ohmic contact with another metal probe because of the iridium oxide surface layer, whereas it would be quit easy to still make a fluidic/ionic contact with the probe. We hope to solve this problem in the near future and move toward totally automating the testing of the STIM-2B (and STIM-3B) probes. With full automation, it should be possible to completely test a probe in 5-10 minutes.

CV Testing

As discussed in previous reports, there is more than one method of activating the iridium sites of an active electrode. Probably the most accurate method is to activate each site individually to a predetermined level, where the accuracy is determined by the frequency of performing CV measurements while delivering activation pulses. The more often the CV characteristic is measured, the more accurately each of the sites can be activated to the target level. The tradeoff is the amount of time the activation process takes for all of the sites, since they must be activated sequentially.

A second method of activating iridium sites is to utilize the POR mode of the probe, which connects all of the sites to the analog I/O pad in parallel thereby allowing them to be activated simultaneously. Obviously, activating 16 sites simultaneously is much faster than activating 16 sites sequentially. The trade-off is that the sites may not activate at the same rate; therefore, they may not end up at the same level of activation or the same site impedance. If there is too much variation between sites, there may be compliance voltage problems or in the case of recording the same signal will be observed to have a different amplitude simply because of the different site impedance.

A third method of site activation is to combine the strengths of the two previous methods. All 16 of the sites are activated in parallel to a level somewhat below the target value and then each site is individually *trimmed* to achieve greater accuracy. This method can be just as accurate as the first provided that there are no sites which activate very quickly and overshoot the target. Obviously though, this method is not as fast as the second since a CV measurement must be made on each of the sites and then activation performed as needed.

In an effort to further compare site activation techniques, more probe channels were activated in the above manners. It was found that the first method of activating sites was extremely time consuming though it was somewhat more accurate than the faster method of activating all of the sites of a channel in parallel. The greatest variation across a single channel when activating the sites in parallel was 3.95% (see Fig. 4), but also in some cases it was as low as 2.06%, where % variation is defined as:

$$\% \text{ variation} = \text{std. dev.}/\text{average}$$

When individually activating each site, the % variation dropped as low as 2.60% when checking the CV between every 50 pulses and allowing a 5% tolerance for when to stop activating; and 0.37% when checking the CV between every 5 pulses. It was also noted that as the level of activation increased, as the number of activating pulses delivered increased, the percentage variation decreased. From the measurements made thus far, it is believed that the best method is to activate the sites in parallel to a given level and then make the individual CV measurements and adjust as necessary. In general, the parallel activation yields activation levels that are close enough for most experiments, but it is a good practice to take the extra time to check the individual CV curves and make any necessary adjustments. We plan to continue to log the results of CV measurements when activating probe sites along with keeping track of the number of pulses required to achieve the level of activation.

Address\Site	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	# Pulses	600
0	NA																	0
1		X																0.164
2			NA															0
3				X														0.146
4					X													0.148
5						X												0.163
6							X											0.158
7								X										0.15
8									X									0.156
9										X								0.159
10											X							0.154

11											X						0.154
12												X					0.148
13													X				0.16
14														X			0.157
15															X		0.146
																Average	**0.155**
																Std Dev.	**0.00610**
																%Variation	**3.947**

Fig. 4: CV measurement data along with the test matrix from channel D of probe #2007.

During the coming quarter, we anticipate running some chronic current pulse tests on STIM-2B of 1 billion+ pulses while monitoring probe and interface system operation and site characteristics. The results of this will provide some interesting data on the longevity of the probes, the system, and the method in which the probes are encapsulated. With the additional new STIM-2B probes that have been etched out, we anticipate doing more *in-vivo* experiments which will involve use of the probes for both stimulation and recording. We also plan to test completed STIM-3B arrays. These arrays will be useful in performing some of the experiments that we have attempted in the past with the 2D STIM-2B arrays and should provide the additional degree of access to tissue heretofore unseen.

4. Development of a 64-Site Active Stimulating Probe with On-Chip Current Generation

For the ultimate implementation of a three-dimensional stimulating probe, STIM-3, its building block, STIM-2, is being redesigned and optimized to ensure full functionality. Several design modifications were suggested and simulated in earlier work. One of them concerns the redesign of the on-chip DAC, which is the most important part of the stimulating probe. Work on the optimization of the DAC continued during the past quarter.

The major concerns in the DAC on the stimulating probe involve the following:

1. maintaining charge balance to avoid any damage to the surrounding tissue; thus, accurate bipolar current generation with matched sourcing and sinking capability is needed in the DAC.
2. achieving high output linearity and low output resistance
3. achieving low power dissipation and layout area from $\pm$5V supplies, and
4. maintaining easy access to DAC calibration.

In the past, three DAC designs have been implemented or proposed for use in the active stimulating electrodes. Fig. 5 shows the simple DAC used in STIM-1, a 16 site active stimulating probe. The reference current here was 8μA. A data bit is used to switch the reference string on/off, and a polarity bit is responsible for selecting either sourcing or sinking current. The output current is almost linearly dependent on the Vdd supply (a 100mV change in Vdd changes the output current by only 5.8%), thus allowing easy calibration of the DAC. The disadvantage of this scheme lies in its power dissipation. Based on this, in STIM-2 (Fig. 6), the latest generation of 64- site 8-channel active probe, the reference string has been redesigned and the voltage across the effective reference string has been reduced by half. Furthermore, the reference current is reduced to 1μA to minimize the power dissipation. However, it is more difficult in this configuration to match the sourcing and sinking currents, complicating DAC calibration. Also, the settling time for the output current is long since the current available to drive the distributed gate capacitance of all the replicate mirroring transistors is limited. Since the sinking current is relatively even smaller than the sourcing current, the pull-down rate in the sinking string is even worse than the sourcing case.

A modification of this scheme is proposed as shown in Fig. 7. Transmission gate between the bias string and mirroring string is utilized here to select sourcing/sinking mode. The reference string is on all the time. This design is upward compatible with what is being used in STIM-2, which is desirable since we want to maintain the other features and data designations used in that design. The DAC Disable function is now implemented by using two PMOS transistors connected with the pass gate transistors. When the select line is tied to ground, the output of the DAC is cut off while the reference current is still on. As in the case of STIM-1, power dissipation in the reference string is a concern here and there exists a trade-off between power consumption and output current settling time when setting the appropriate reference current.. As shown in Fig 8, the sinking current pull down rate suffers substantially with a small reference current. With a reference current of 3μA, the settling time is reasonable. Taking into account that there are 8 DACs on STIM-2 and even more on STIM-3, and that the typical stimulating pulse widths are around 200μs compared to the settling time of a few microseconds, 3μA appears to be an acceptable target for the reference current. A detailed schematic is shown in Fig 9. This design appears to be an acceptable compromise between the designs of STIM-1 and STIM-2 and will be pursued for the redesigned STIM-2/3. We hope to complete the design optimization during the next term, adding features such as a multi-level interpulse bias level for the sites and a separate dedicated output line for the recording function.

Fig. 5: A simple schematic of the STIM-1 DAC

Fig. 6: Schematic of the STIM-2 DAC

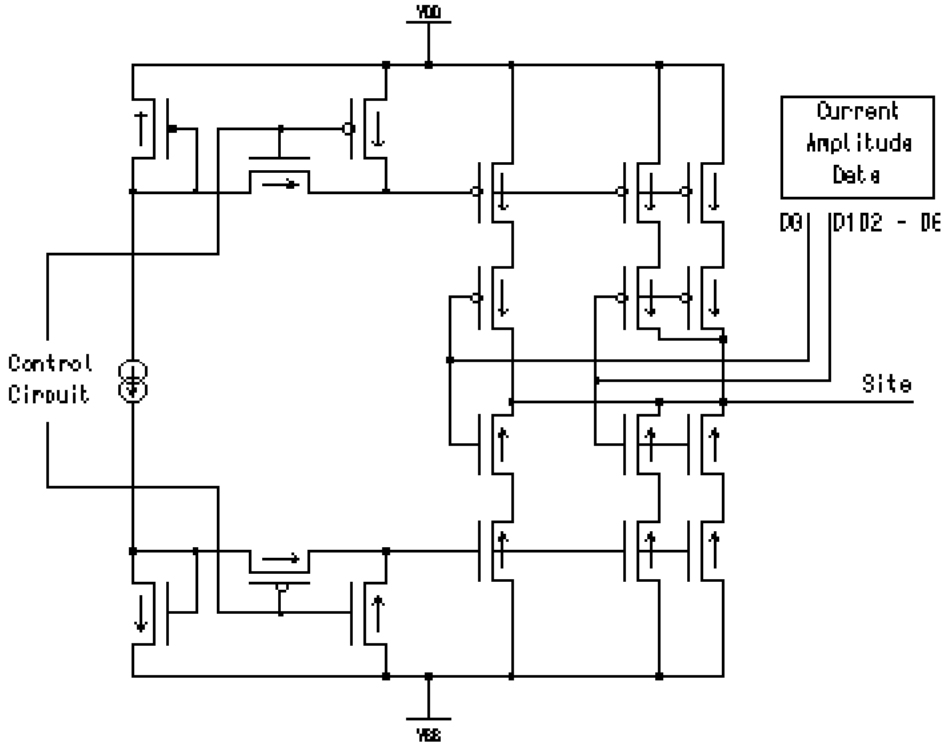

Fig. 7: Proposed DAC circuit for a revised STIM-2.

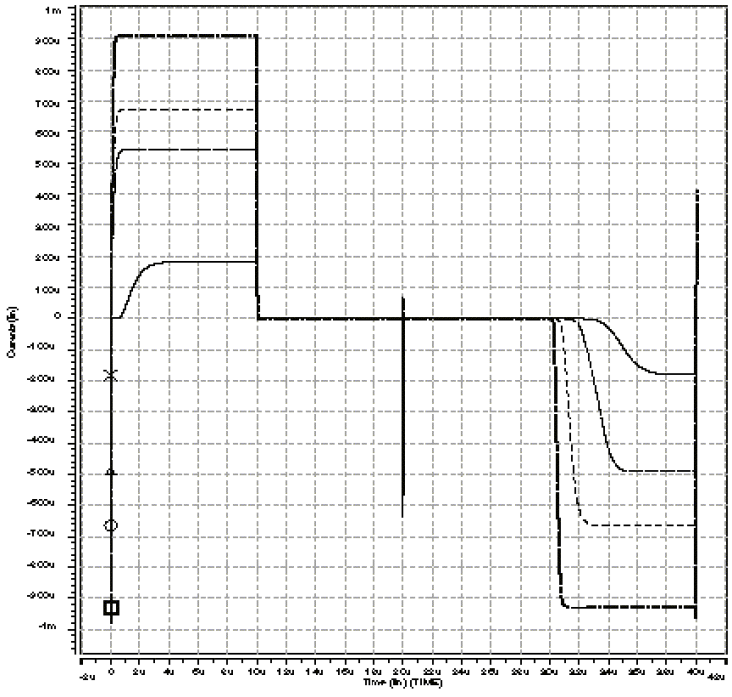

Fig. 8: Simulation of the proposed DAC for STIM-2/-3 for various reference current bias levels.

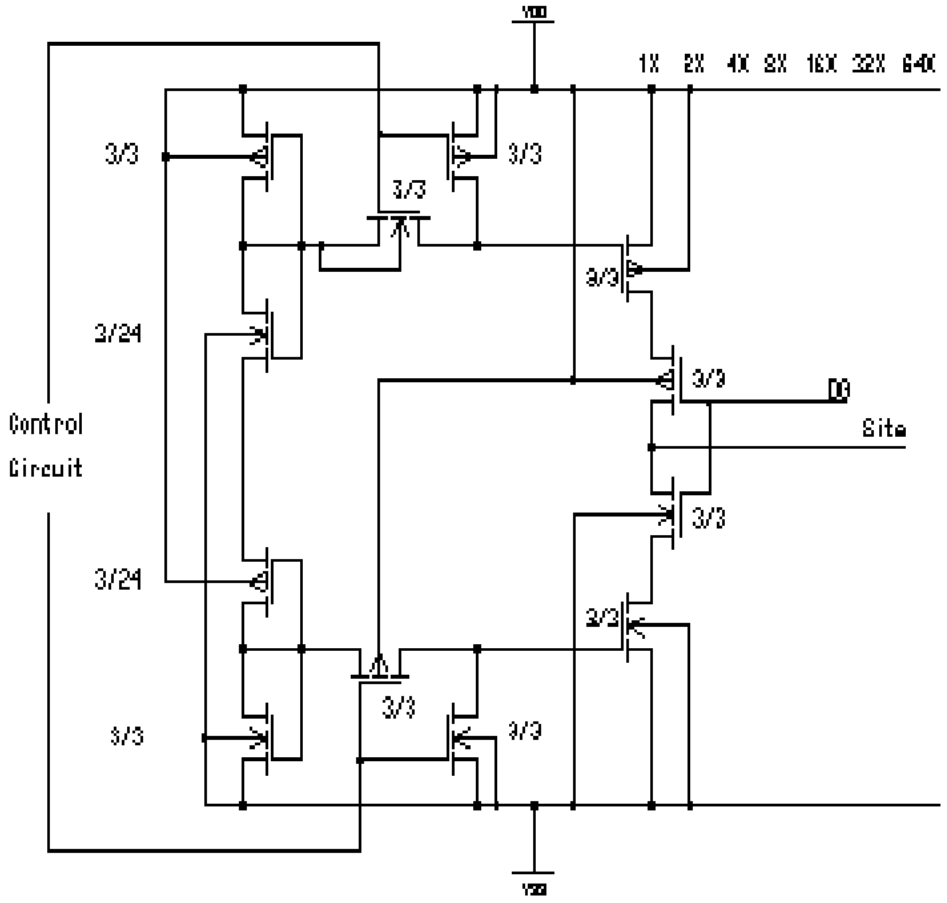

Fig. 9: More detailed schematic of the redesigned DAC for STIM-2/-3. The reference current here is set at 3µA.

6. Conclusions

During the past term, we have continued to fabricate passive probes for a variety of users and have begun to tackle the detailed problems associated with testing the active probes prior to use. Using the external user interface system, a test probe was tested with over 60 million pulses without failure, addressing the probe at the maximum rate achievable by the external board (9.5MHz). Additional long-term tests of these probes, running over one billion 100µA current pulses, will be performed during the coming term. Work on appropriate testing jigs and testing software protocols has reduced the testing

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